AF/1653

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**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

| | | |
|---|---|---|
| *In re* Reissue Application of | ) | |
| | ) | Group Art Unit: 1653 |
| VINIK *et al.* | ) | |
| | ) | Examiner: H. A. Robinson |
| Serial No. 09/659,379 | ) | |
| reissue of U.S. Patent 5,804,421 | ) | |
| | ) | Atty. Dkt. No. 005126.00003 |
| Filed: September 8, 2000 | ) | |

For: **High Level of Expression of INGAP in Bacterial and Eukaryotic Cells**

**TRANSMITTAL OF SUBSTITUTE BRIEF ON APPEAL**

Mail Stop Appeal Brief - Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, Va 22313-1450

Sir:

In response to the Notification of Non-Compliance with 37 C.F.R. § 1.192(c) mailed May 26, 2004, Appellants submit an original and two copies of a substitute Brief on Appeal. We believe no fee is due in connection with this response. If a fee is due, please charge our Deposit Account No. 19-0733.

## Remarks

The Notification of Non-Compliance asserts various reasons why the Brief on Appeal filed March 22, 2004 did not comply with 37 C.F.R. § 1.192(c). The substitute Brief on Appeal addresses these reasons as follows:

- the filing date of co-pending application Serial No. 09/717,095 has been added;
- the statement regarding status of the claims has been expanded as requested in the Notification;
- the issue to be decided by the Board has been rephrased;
- the Table of Contents, which is not required under 37 C.F.R. § 1.192(c), has been deleted; and
- the claims appealed in the present application and those pending in the appeal of Serial No. 09/717,095) are presented in two Appendices, and the format of the claims has been changed to put them in proper appeal format.[1]

The original Brief and the substitute Brief state that rejected claims 1-49 stand or fall together in the following groups:

- claims 1-20 and 23-48; and
- claims 21, 22, and 49.

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[1] In a telephone conference held June 24, 2004, William Dixon, reissue specialist for Group 1600, advised Appellants to include the appealed claims in two appendices. One appendix contains a clean copy of the appealed claims. The other appendix shows the appealed claims as they differ from the issued patent. Mr. Dixon advised Appellants that neither set of claims should include parenthetical expressions after the claim numbers (*i.e.*, because the Appeal Brief is not an amendment, indications of how many times the claims have been changed should be included).

The Notification of Non-Compliance asserts that "the information provided under this heading [*i.e.*, "Grouping of the Claims"] in the instant application [sic; Brief] is insufficient." Notification of Non-Compliance at page 3, first paragraph. The Notification also asserts that the original Brief did not present arguments to support grouping claims 1-49 into two groups.

Both the original and the substitute Brief present separate arguments for each of the two groups of claims with respect to the double patenting rejection. See sections B.2.a, b.2.b, B.2.c, and C. Both the original and the substitute Brief set forth facts underlying the arguments for separate patentability. See sections A.1.a, A.1.b, and A.3. The substitute Brief also points out these sections under the heading "Grouping of the Claims," as the Examiner requested.

Respectfully submitted,
BANNER & WITCOFF, LTD.

Date: June 25, 2004

By: Lisa M. Hemmendinger
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OIPE JC17
JUN 25 2004
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PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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| *In re* Reissue Application of | ) | |
| | ) | Group Art Unit: 1653 |
| VINIK *et al.* | ) | |
| | ) | Examiner: H. A. Robinson |
| Serial No. 09/717,095 | ) | |
| reissue of U.S. Patent 5,840,531 | ) | |
| | ) | Atty. Dkt. No. 005126.00001 |
| Filed: November 22, 2000 | ) | |

For: **INGAP PROTEIN INVOLVED IN PANCREATIC ISLET NEOGENESIS**

**SUBSTITUTE BRIEF ON APPEAL**

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OIPE JC177
JUN 25 2004
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
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For: **INGAP PROTEIN INVOLVED IN PANCREATIC ISLET NEOGENESIS**

## SUBSTITUTE BRIEF ON APPEAL

U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, Mail Stop Appeal Brief - Patents
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Appellants submit an original and two copies of this substitute Brief on Appeal. Appellants filed the original Brief on Appeal on March 22, 2004. A Notification of Non-Compliance with 37 C.F.R. § 1.192(c) was mailed May 26, 2004. We believe no fee is due in connection with this substitute brief. If a fee is due, however, please charge it to our Deposit Account No. 19-0733.

## REAL PARTIES IN INTEREST

The real parties in interest in this reissue application are McGill University and Eastern Virginia Medical School of the Medical College of Hampton Roads, to which this application is assigned.

## RELATED APPEALS AND INTERFERENCES

Claims in the present application have been rejected as obvious over those pending in Serial No. 09/659,379 filed September 8, 2000, which is a reissue application of U.S. Patent 5,804,421. A corresponding rejection has been made in Serial No. 09/659,379 and has been appealed.

## STATUS OF CLAIMS

Claims 1-24 were originally filed in the present application. During prosecution, claims 1, 2, 5, 8, 10, 12, 13, 15-17, and 24 were amended. Claims 1-24 are now pending and are appealed. A clean copy of the appealed claims is attached as Appendix 1; a copy of the appealed claims as they differ from issued U.S. Patent 5,840,531 is attached as Appendix 2.

## STATUS OF AMENDMENTS

Claims 12, 17, and 24 were amended in the response filed November 26, 2003 under 37 C.F.R. § 1.116. An Advisory Action mailed December 31, 2003 indicated that the amendments would be entered. Appendices 1 and 2 reflect the claims as amended in the November 26 response.

## SUMMARY OF THE INVENTION

One embodiment of the invention is an isolated DNA molecule encoding a mammalian islet cell neogenesis associated protein (INGAP) which has the amino acid sequence shown in SEQ ID NO:2. Col. 1, lines 29-31; col. 5, lines 63-65.[1] The DNA molecule can be present in a vector which can comprise expression control sequences for expression in a host cell. Col. 6, lines 10-12. A host cell can be transformed with the isolated DNA molecule encoding mammalian INGAP having the amino acid sequence shown in SEQ ID NO:2 or with a vector comprising the isolated DNA molecule. Col. 6, lines 10-39.

Another embodiment of the invention is a nucleotide probe comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian INGAP having the sequence shown in SEQ ID NO:2. Col. 6, lines 40-41.

Another embodiment of the invention is an isolated DNA molecule comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian INGAP having the sequence shown in SEQ ID NO:2. The DNA molecule encodes a polypeptide which stimulates islet cell neogenesis. Col. 23, lines 43-46.

Another embodiment of the invention is a method of producing a mammalian INGAP. A host cell comprising an isolated DNA molecule encoding a mammalian INGAP is cultured in a nutrient medium so that the mammalian INGAP is expressed. The INGAP is harvested from the host cell or the nutrient medium. Col. 7, lines 35-43.

Another embodiment of the invention is an antisense construct of a mammalian INGAP gene. The antisense construct comprises a promoter, a terminator, and a nucleotide sequence

[1] All references are to the specification of U.S. Patent 5,840,531.

which encodes all or a portion of a protein as shown in SEQ ID NO:2. The nucleotide sequence is between the promoter and the terminator and is inverted with respect to the promoter. An mRNA complementary to native mammalian INGAP mRNA is produced upon expression from the promoter, and the mRNA prevents translation of the native mammalian INGAP mRNA. Col. 8, lines 50-56.

## ISSUE

Whether claims 1-24 are properly rejected under the judicially created doctrine of obviousness-type double patenting.

## GROUPING OF CLAIMS

The claims stand or fall together in the following groups:

- 1-8, 15, 16, and 18-22; and
- claims 9-14, 17, 23, and 24.

The Brief sets forth facts underlying the arguments for separate patentability in sections A.1.a and A.1.b.

The Brief presents separate arguments for these groups of claims with respect to the double patenting rejection in sections C.1, C.2a, C.2b, C.2c, and D. As explained in section B, a two-way obviousness test must be applied. Under the two-way test, if either of two sets of claims is not obvious over the other, no rejection for double-patenting should be made in either case. Each of cited claims 1-49 of Serial No. 09/659,379 excludes a nucleotide sequence

encoding the INGAP signal sequence. Claims 1-8, 15, 16, and 18-22 of the present application cannot teach or suggest removing the amino acids of the signal sequence from the recited amino acid sequence because claims 1-8, 15, 16, and 18-22 explicitly require a nucleotide sequence encoding the full-length INGAP pre-protein. Claims 9-14, 15, 16, and 18-22 of the present application cannot teach or suggest removing the amino acids of the signal sequence from the recited amino acid sequence because claims 9-14, 15, 16, and 18-22 do not recite any particular portion of SEQ ID NO:2 that should be included or excluded. Thus, neither claims 1-8, 15, 16, and 18-22 nor claims 9-14, 17, 23, and 24 teach or suggest all the elements in claims 1-49 of the 09/659,379 application.

## ARGUMENT

Application of the required two-way obviousness test and the *Graham v. John Deere Co.* factors to properly construed claims compels the conclusion that claims 1- 24 and claims 1-49 are not obvious over each other.

Claims 1-24 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-49 of co-pending application Serial No. 09/659,379. A proper analysis of the facts, however, reveals no legal or factual basis for the double patenting rejection.

A. Every limitation is material to properly construe claims 1-8, 15, 16, and 18-22 and claims 9-14, 17, 23, and 24 of the present application and claims 1-49 of Serial No. 09/659,376.

The question of whether the obviousness-type double patenting rejection is correct cannot be answered without properly construing the claims in both applications: "Double patenting is altogether a matter of what is claimed." *General Foods Corp. v. Studiengesellschaft Kohle GmbH*, 972 F.2d 1272, 1277, 23 U.S.P.Q.2d (BNA) 1839, 1343 (Fed. Cir. 1992). It is a fundamental rule of claim construction that every limitation is material and that what is claimed is what is defined by the claim as a whole. *Id.* at 1280, 23 U.S.P.Q.2d (BNA) at 1845.

1. Neither claims 1-8, 15, 16, and 18-22 nor claims 9-14, 17, 23, and 24 of the present application teaches excluding a nucleotide sequence that encodes the INGAP signal sequence.

Proper construction of claims 1-8, 15, 16, and 18-22 and of claims 9-14, 17, 23, and 24 of the present application reveals that none of these claims teaches excluding a nucleotide sequence that encodes the INGAP signal sequence.

a. Claims 1-8, 15, 16, and 18-22 explicitly require a nucleotide sequence encoding the full-length INGAP pre-protein.

Claims 1, 2, 18, 19, and 22 of the present application are directed to isolated DNA molecules encoding a mammalian islet cell neogenesis associated protein (INGAP) which has the amino acid sequence shown in SEQ ID NO:2. SEQ ID NO:2 is the amino acid sequence of full-length INGAP pre-protein (*i.e.*, including its signal sequence). Claims 3-5 and 20 are directed to vectors comprising the isolated DNA. Claims 6-8 and 21 are directed to host cells comprising the vectors. Claims 15 and 16 are directed to methods of using the host cells to produce full-length INGAP pre-protein. Thus, each of claims 1-8, 15, 16, and 18-22 explicitly recites a DNA molecule encoding the full-length INGAP pre-protein, including the signal sequence.

b. Claims 9-14, 17, 23, and 24 do not recite any particular portion of the full-length INGAP pre-protein coding sequence.

Claims 9-11 are directed to nucleotide probes comprising at least 30 contiguous nucleotides of a sequence encoding INGAP; the INGAP has the amino acid sequence shown in SEQ ID NO:2. Claims 12-14, 23, and 24 are directed to isolated DNA molecules comprising at least 30 contiguous nucleotides of a sequence encoding INGAP; the INGAP has the amino acid sequence shown in SEQ ID NO:2. Claim 17 is directed to an antisense construct of INGAP. The antisense construct comprises a promoter, a terminator, and a nucleotide sequence which encodes all or a portion of SEQ ID NO:2. The nucleotide sequence is between the promoter and the terminator and is inverted with respect to the promoter. An mRNA complementary to native mammalian INGAP mRNA is produced upon expression from the promoter, and the mRNA

prevents translation of the native mammalian INGAP mRNA. None of claims 9-14, 17, 23, or 24 recites any particular portion of SEQ ID NO:2 that should be included or excluded in the claimed probes, DNA molecules, or antisense constructs.

2. Each of claims 1-49 of Serial No. 09/659,379 explicitly excludes a nucleotide sequence encoding the INGAP signal sequence.

Serial No. 09/659,379 presents 49 claims, which are reproduced in Appendices 3 (clean copy) and 4 (claims as they differ from issued U.S. Patent 5,804,421).[2] Claims 1, 13, 15, 21, 23, 29, 45, and 47 are independent. Construction of the independent claims is sufficient to illuminate the key differences between claims 1-49 of Serial No. 09/659,379 and claims 1-24 of the present application.

a. Independent claims 1, 13, 15, 23, 29, 45, and 47 explicitly exclude a nucleotide sequence encoding the INGAP signal sequence.

Independent claim 1 is directed to a recombinant construct for expression of a protein which stimulates islet cell neogenesis. Independent claim 13 is directed to a method of producing biologically active INGAP using the same recombinant construct. Independent claim 15 is directed to a host cell comprising the same recombinant construct. The recombinant construct recited in claims 1, 13, and 15 comprises a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO:6 operably linked to a transcriptional initiation site and a translational initiation site. SEQ ID NO:6 is the amino acid sequence of human

[2] An amendment filed together with the Brief on Appeal in Serial No. 09/659,379 corrects a minor clerical error in claims 16-18, 21, 23, 27, 29, and 45 (correcting the recitation of nucleotides "12-456" to "12-458"). The appealed claims as discussed in this Brief and as set forth in Appendices 3 and 4 reflect the correction.

INGAP. SEQ ID NO:6 includes amino acids 1-26, which is INGAP's signal sequence. See col. 2, lines 33-34 of U.S. Patent 5,804,421.

The recited recombinant construct explicitly does not contain a particular recited sequence, *i.e.*, a sequence encoding the amino acids of the signal sequence of INGAP. See claim 1, lines 5-6; claim 13, lines 5-7; and claim 15, lines 3-5: "wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5' of said first nucleotide sequence."

Independent claim 23 is directed to a method of making an expression construct. The method recites linking a transcription initiation site, a translation initiation site, and a coding sequence for mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO:4 to make an expression construct. "Mature" human INGAP does not contain a signal sequence. See U.S. Patent 5,804,421 at col. 4, lines 43-46: "This example describes the use of polymerase chain reaction to synthesize INGMAT (a construct which lacks the signal peptide sequence, i.e., which encodes the mature protein)." Nucleotides 12 to 458 of SEQ ID NO:4 do not include nucleotides that encode the signal sequence of INGAP. See U.S. Patent 5,804,421 at col. 5, lines 34-37: "At the end of this step the sequence of the PCR product that contains both restriction sites minus the signal sequence and 5' UTR was as follows (SEQ ID NO: 4) . . . ." Claim 23 explicitly states that the resultant expression construct is "devoid of the signal sequence of the coding sequence of INGAP." Claim 23, lines 4-5.

Independent claim 29 is directed to a recombinant construct. Independent claim 45 is directed to a method of producing biologically active INGAP using the same recombinant construct. The recombinant construct recited in claims 29 and 45 comprises a first nucleotide

sequence encoding mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO:4 operably linked to a transcriptional initiation site and a translational initiation site. Independent claim 47 is directed to a host cell comprising a recombinant construct. The recombinant construct comprises a first nucleotide sequence encoding mature human INGAP operably linked to a transcriptional initiation site and a translational initiation site.

The recombinant constructs recited in claims 29, 45, and 47 explicitly do not contain a particular recited sequence: "a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5′ of said first nucleotide sequence."

Thus, each of independent claims 1, 13, 15, 23, 29, 45, and 47 contains an explicit negative limitation that requires the absence of a particular recited element.

b. The pair of primers recited in independent claim 21 amplifies an INGAP coding sequence that explicitly excludes the INGAP signal sequence.

A corresponding negative limitation is inherent in independent claim 21. Independent claim 21 is directed to a pair of primers for amplifying a coding sequence consisting of nucleotides 12 to 458 of SEQ ID NO:4. As explained above, SEQ ID NO:4 of Serial No. 09/659,379 is a nucleotide sequence lacking the 5′ untranslated region and encoding mature human INGAP, *i.e.*, INGAP without its signal sequence.

Each of the oligonucleotide primers hybridizes to an opposite strand of a double-stranded INGAP template under conditions sufficient for amplifying. The first primer hybridizes to the 5′ end of the coding sequence for mature human INGAP. The second primer hybridizes to the 3′ end of the nucleotide sequence encoding mature human INGAP. Hybridization takes place under conditions sufficient for amplifying nucleotides 12 to 458 of SEQ ID NO:4.

The meaning of the term "consisting of" has long been understood to exclude any element not specified in the claim. *In re Gray*, 53 F.2d 520, 521, 11 U.S.P.Q. (BNA) 255, 256 (C.C.P.A. 1931). Thus, the closed term "consisting of" in claim 21 means that the amplified sequence includes only the recited nucleotides 12 to 458 of SEQ ID NO:4, *i.e.*, a sequence that encodes mature INGAP without its signal peptide.[3]

3. The Examiner erroneously construed claims 1-49 of Serial No. 09/659,379 to include the INGAP signal sequence.

The present application claims DNA molecules encoding INGAP (claims 1, 2, 18, 19, and 22), vectors containing the DNA molecules (claims 3-5 and 20), host cells containing the vectors or the DNA molecules (claims 6-8 and 21), and methods of producing INGAP using the host cells (claims 15 and 16). Proper construction of claims 1-8, 15, 16, and 18-22 must include the fact that these claims must have a nucleotide sequence encoding the INGAP pre-protein, which includes its signal sequence.

The present application also claims probes (claims 9-11), antisense constructs (claim 17), and DNA molecules comprising at least a portion of an INGAP coding sequence (claims 12-14, 23, and 24). Proper construction of claims 9-14, 17, 23, and 24 must recognize the fact that none of these claims specifies a nucleotide sequence that encodes any particular portion of INGAP.

Serial No. 09/569,379 claims recombinant constructs, host cells comprising the recombinant constructs, methods of producing biologically active INGAP using the recombinant constructs, methods of making expression constructs, and primers for amplifying the coding portion of the expression or recombinant constructs. Each of the recited constructs explicitly

[3] The Appellants of Serial No. 09/659,379 do not concede by this statement that they are not entitled to equivalents of nucleotides 12 to 458 of SEQ ID NO:4.

includes a coding sequence for mature INGAP which lacks the signal sequence. Each of the recited constructs explicitly excludes a coding sequence for the signal sequence. Proper construction of claims 1-49 must include the fact that the claims exclude from their scope constructs containing a coding sequence for the INGAP signal sequence.

The Examiner has ignored the plain language of the claims throughout the prosecution of the present application. Contrary to the basic canons of claim construction, the Examiner asserts that use of the open term "comprising" permits her to ignore the claims' explicit negative limitations. See the Advisory Action mailed December 31, 2003:

> The issue here remains that the claims in the copending application recite the open language "comprising" in association with the recitation of "residues 27-175", thus, **residues 1-26 are not really excluded as asserted by applicant.**

Advisory Action at page 3, lines 12-15, emphasis added. Addressing Appellants' response after final rejection filed November 26, 2003, the Examiner states:

> Again the argument is made that residues 1-26 of SEQ ID NO:2 in the instant application is [sic; are] excluded from SEQ ID NO:6 of the copending application, **which is not factual as the claim recites open language which would include those residues.**

Advisory Action at page 4, lines 7-9, emphasis added.

The Examiner's construction of claims 1-49 of Serial No. 09/659,379 violates the fundamental rule of claim construction that all parts of the claim must be considered. *General Foods*, 972 at 1280, 23 U.S.P.Q.2d (BNA) at 1845. There is no legal basis for ignoring the exclusion of the second nucleotide sequence from the constructs recited in independent claims 1, 13, 15, 23, 29, 45, and 47 or for ignoring the closed language of claim 21. Absent a failure to comply with 35 U.S.C. § 112, every portion of the claim must be considered when determining

whether an invention is obvious. *In re Duva*, 387 F. 2d 402, 407, 156 U.S.P.Q. (BNA) 90, 94 (C.C.P.A. 1967).

There has been no rejection based on the negative limitations or closed language under 35 U.S.C. § 112, first or second paragraph; thus, the Examiner has acknowledged that these recitations are supported in the specification and are definite. Both the negative limitations and basis for the recitation "consisting of" have clear support in the specification of Serial No. 09/659,379. *See* U.S. Patent 5,804,421 at col. 1, lines 58-60, and Examples 1 and 2.

In fact, the M.P.E.P. explicitly authorizes use of negative limitations provided the claim is otherwise clear:

> A fundamental principle contained in 35 U.S.C.112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art. **Applicant may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the present matter for which protection is sought.** As noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the present matter for which patent protection is sought.

M.P.E.P. § 2173.01, emphasis added. As noted above, the Examiner has not alleged that the negative limitations of claims 1, 13, 15, 23, 29, 45, and 47 or the closed language of claim 21 make claims 1-49 of Serial No. 09/569,379 in any way indefinite.

The Examiner's erroneous dismissal of the recited negative limitations of claims 1, 13, 15, 23, 29, 45, and 47 and the closed language of claim 21 has prevented the correct analysis of the asserted double patenting rejection. "Double patenting is based entirely on *what* is claimed,

reading each claim as an entirety to determine what invention it defines." *General Foods*, 972 F.2d at 1281, 23 U.S.P.Q.2d (BNA) at 1845, emphasis in original.

B. A two-way obviousness test must be applied because the two inventions could not have been filed in one application and because the U.S. Patent and Trademark Office caused administrative delay in the issuance of the earlier-filed application.

Having properly construed the claims of each application, a two-way obviousness test must be applied to assess the alleged double patenting. The two-way test applies if (1) administrative delay on the part of the Office caused delay in prosecution of the earlier filed application; and (2) applicant could not have filed the conflicting claims in a single (*i.e.*, the earlier filed) application. *In re Berg*, 140 F.3d 1428, 1437, 46 U.S.P.Q.2d (BNA) 1226, 1233 (Fed. Cir. 1998). The present application meets both prongs for the two-way test.

First, there was administrative delay. The present application is a reissue application of U.S. Patent 5,840,531. There was administrative delay in the prosecution of the underlying application that issued as U.S. Patent 5,840,531. Application Serial No. 08/709,662, which issued as U.S. Patent 5,840,531, was filed September 9, 1996, claiming benefit of a February 22, 1995 priority date. Application Serial No. 08/909,725, the application underlying the cited co-pending application Serial No. 09/659,379, was filed August 12, 1997, claiming priority to an October 30, 1996 application. The later-filed underlying application (08/909,725) issued first. Appellants caused no delay in the 09/709,662 application. The relevant dates are tabulated below.

| **Serial No.** | **Filing Date** | **Priority Date** | **Issue Date** |
|---|---|---|---|
| 08/709,662 | September 9, 1996 | February 22, 1995 | November 24, 1998 |
| 08/909,725 | August 12, 1997 | October 30, 1996 | September 8, 1998 |

The earlier issuance of the later-filed 08/909,725 application evidences the Patent and Trademark Office's administrative delay in examination of the earlier-filed 08/709,662 application.

Second, Appellants could not have filed the two sets of claims in the earlier filed 08/709,662 application. The invention claimed in Serial No. 08/909,725 is not disclosed in either the 08/709,662 or its parent application. In fact, the invention claimed in Serial No. 08/909,725 had not yet been invented on February 22, 1995. A declaration of Dr. Aaron Vinik regarding the relative dates of invention was enclosed with the response filed November 26, 2003.

Both prerequisites for application of the two-way test are satisfied; thus, the two-way test must be applied. When the two-way test is applied, if either of the two sets of claims is not obvious over the other, no rejection for double-patenting should be made in either application. M.P.E.P., 8th ed., § 804 (II)(B)(1)(b).

C. Application of the *Graham* factors under the two-way test compels a conclusion that claims 1-8, 15, 16, and 18-22 and claims 1-49 are not obvious over each other and that claims 9-14, 17, 23, and 24 and claims 1-49 are not obvious over each other.

An obviousness-type double patenting rejection is analogous to an obviousness rejection under 35 U.S.C. § 103 except that the disclosure of the cited patent is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 600, footnote 4, 154 U.S.P.Q. (BNA) 29, 34, footnote 4 (C.C.P.A. 1967). Thus, the double patenting analysis parallels an analysis under 35 U.S.C. § 103(a). *In re Braat,* 937 F.2d 589, 592, 19 U.S.P.Q.2d (BNA) 1289, 1291-92 (Fed. Cir. 1991).

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

*Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. M.P.E.P., 8th ed., § 2142. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

*Id.*

The *Graham* obviousness analysis is applied twice when making a two-way obviousness determination. M.P.E.P. § 804 (II)(B)(1)(b). When the two-way test is applied, if either of the two sets of claims is not obvious over the other, no rejection for double-patenting should be made in either application. *Id.* While Appellants do not concede that claims 1-24 are obvious variants of the invention claimed in Serial No. 09/659,379, it is sufficient under the two-way test to demonstrate that claims 1-49 of Serial No. 09/569,379 are not obvious variants of the invention claimed in the present application. The results of the factual inquiries under *Graham* provide this demonstration.

1. The scope and content of the "prior art" (claims 1-8, 15, 16, and 18-22 and claims 9-14, 17, 23, and 24 and of the present application) do not teach or suggest excluding the signal sequence to achieve high levels of INGAP expression.

The first factual inquiry under *Graham* is to determine the scope and content of the prior art. 383 U.S. at 17. There is no "prior art" in an obviousness-type double patenting rejection; only the claims of the cited patent are available for use as the basis of the rejection. *Braithwaite*, 379 F.2d at 600, 154 U.S.P.Q. (BNA) at 34.

Claims 1-8, 15, 16, and 18-22

None of claims 1-8, 15, and 16 and 18-22 recites the mature, processed form of INGAP. There is no recitation in any of claims 1-8, 15, 16, or 18-22 that excludes a nucleotide sequence encoding the INGAP signal sequence or that hints or suggests there is any benefit or advantage to excluding the signal sequence. On the contrary, each of claims 1-8, 15, 16, and 18-22 explicitly recites DNA molecules encoding the full-length INGAP pre-protein, which includes the signal sequence.

Claims 9-14, 17, 23, and 24

Claims 9-11 are directed to nucleotide probes comprising at least 30 contiguous nucleotides of a sequence encoding INGAP pre-protein; the INGAP pre-protein has the amino acid sequence shown in SEQ ID NO:2, which includes the signal sequence. Claims 12-14, 23, and 24 are directed to isolated DNA molecules comprising at least 30 contiguous nucleotides of a sequence encoding INGAP; the INGAP has the amino acid sequence shown in SEQ ID NO:2, which includes the signal sequence. Claim 17 is directed to an antisense construct of INGAP comprising a promoter, a terminator, and a nucleotide sequence which encodes all or a portion of SEQ ID NO:2, which includes the signal sequence.

There is no recitation in any of claims 9-14, 17, 23, or 24 excluding a nucleotide sequence encoding the INGAP signal sequence. None of claims 9-14, 17, 23, or 24 recites the mature, processed form of INGAP. None of claims 9-14, 17, 23, or 24 contains a hint or suggestion that there is any benefit or advantage to excluding the signal sequence.

2. There are critical differences between claims 1-8, 15, and 16 and 18-22 of the present application and claims 1-49 of Serial No. 09/659,379 and critical differences between claims 9-14, 17, 23, or 24 and claims 1-49 of Serial No. 09/659,379.

There are critical differences between the subject matter claimed in Serial No. 09/659,379 and that claimed in the present application.

a. Claims 1-8, 15, and 16 and 18-22 of the present application explicitly require a nucleotide sequence encoding the full-length INGAP pre-protein, whereas claims 1-49 explicitly exclude a nucleotide sequence encoding the INGAP signal sequence.

There is no overlap between the subject matter of claims 1-8, 15, 16, and 18-22 of the present application and claims 1-49 of Serial No. 09/659,379. Each of claims 1-49 of Serial No.

09/659,379 explicitly excludes a nucleotide sequence encoding amino acid residues 1-26 of SEQ ID NO:6 (*i.e.*, of the pre-protein). In contrast, the constructs recited in each of claims 1-8, 15, 16, and 18-22 of the present application explicitly include a nucleotide sequence encoding the full-length INGAP pre-protein, *i.e.*, including the amino acid residues of the signal sequence (residues 1-25 of SEQ ID NO:2).[2]

b. Claims 9-14, 17, 23, and 24 of the present application do not recite any particular portion of the full-length INGAP pre-protein coding sequence, whereas claims 1-49 explicitly exclude a nucleotide sequence encoding the INGAP signal sequence.

The scope of claims 1-49 of Serial No. 09/569,379 excludes a nucleotide sequence encoding the INGAP signal sequence. Claims 9-14, 17, 23, and 24 of the present application do not specify or suggest exclusion of any portions of a nucleotide sequence encoding full-length INGAP pre-protein. None of claims 9-14, 17, 23, or 24 points in any way to exclusion of the signal sequence.

c. The Examiner has repeatedly mischaracterized the differences between the claimed subject matter in the two applications.

Throughout the prosecution of the present application, the Examiner has incorrectly characterized the difference between claims 1-24 and claims 1-49 of Serial No. 09/569,376. First, the Examiner has ignored the plain language of claims 1-49 of Serial No. 09/569,379 and mischaracterized the claimed subject matter:

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[2] The number of amino acids in the signal sequence differs between the two applications due to the difference in the assignment of the first codon. The present application discloses only a single methionine residue at the N-terminus of the pre-protein, whereas Serial No. 09/659,379 discloses two methionine residues at the N-terminus.

> Although the claims are not identical, they are not patentably distinct from each other because the claims in the copending application are directed to a recombinant construct for expression of INGAP which comprises a nucleotide sequence that encodes the amino acids set forth in SEQ ID NO: 6.

Paper No. 19 at page 4, lines 12-15. As explained above, however, none of claims 1-49 is directed to a nucleotide sequence encoding all of SEQ ID NO:6 (which includes the signal sequence). Each of claims 1-49 explicitly excludes a nucleotide sequence encoding the portion of SEQ ID NO:6 that is the signal sequence.

Second, the Examiner erroneously compares recited sequences in sequence listings rather than comparing the properly construed claims. The Examiner compares SEQ ID NO:2 of the present application to SEQ ID NO:6 of Serial No. 09/569,376 and finds that they differ by only a single amino acid, a methionine:

> Note that the present application is directed to an isolated DNA molecule which encodes an INGAP protein set forth in SEQ ID NO: 2 and both sequences are identical with the exception of one residue (SEQ ID NO: 6 has an additional Methionine in the beginning of the sequence.)

Paper No. 19, at page 4, lines 15-18. But mere comparison of sequences in sequence listings does not accomplish a comparison of claimed subject matter. A proper comparison must be made between the recited subject matter of the two sets of claims. "[A] double patenting rejection must rely on a comparison with the claims in an issued or to be issued patent." M.P.E.P. § 804 (III). Moreover, all of the claim limitations must be considered. *General Foods*, 972 F.2d at 1280, 23 U.S.P.Q.2d (BNA) at 1845. If one compares the claimed subject matter in the two applications, considering all of the recitations of the claims, one finds a much larger difference between the claims of the two applications than the Examiner has

acknowledged. The claims of Serial No. 09/569,379 exclude a nucleotide sequence encoding amino acid residues 1-26 of SEQ ID NO:6 (*i.e.*, of the pre-protein). Each of claims 1-8, 15, 16, and 18-22 of the present application explicitly requires a nucleotide sequence encoding the pre-protein, *i.e.*, including residues 1-25 of SEQ ID NO:2. Each of claims 9-14, 17, 23, and 24 explicitly recites a nucleotide sequence encoding the pre-protein. Thus the subject matter of claims 1-8, 15, 16, and 18-22 and the subject matter of claims 9-14, 17, 23, and 24 are far more distinct and non-overlapping with that of claims 1-49 of Serial No. 09/569,376 than a single methionine residue.

Third, the Examiner mischaracterizes the general subject matter of each application.

> Furthermore, the present application and copending application both claim probes, primers, and have claims directed to antisense strands which would render each other obvious.

Paper No. 19, page 4, line 18, to page 5, line 1. This statement is incorrect. The present application contains claims to probes (claims 9-11) and antisense constructs (claim 17), but not to primers. Serial No. 09/569,379 has claims to primers (claims 21, 22, and 49) but not to probes or antisense constructs. Thus, the subject matter of the claims in the two applications does not overlap in the manner the Examiner asserts.

3. The hypothetical person of ordinary skill in the art would have known that the effect of excluding a signal sequence on protein expression is unpredictable.

The third factual inquiry under *Graham v. John Deere Co.* is to resolve the level of skill in the pertinent art. 383 U.S. at 17. The person of ordinary skill is described in *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*:

> The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual

> inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such factors may be present in every case, and one or more of them may predominate.

807 F.2d 955, 962-63, 1 U.S.P.Q.2d (BNA) 1196, 1201 (Fed. Cir. 1986).

At the priority dates of the present application and of Serial No. 09/569,379, the hypothetical person of ordinary skill would have been aware of all pertinent prior art relating to expression of cloned genes in heterologous host cells. The person of ordinary skill would have known that the effect of excluding a signal sequence in the protein to be expressed was unpredictable. This unpredictability is evidenced by the following three publications, each of which was enclosed with the response filed November 26, 2003.

Xu *et al.,* "The role of the leader sequence coding region in expression and assembly of bacteriorhodopsin," *J. Biol. Chem. 270:* 24858-24863, 1995, describes the deletion of a 13-amino acid signal sequence (leader sequence) in a rhodopsin protein. The deletion of the leader resulted in unstable mRNA and almost no rhodopsin protein production. See Abstract. Xu postulates that the loss of protein production is due to degradation of the mRNA.

Jarvis *et al.*, "Influence of different signal peptides and prosequences on expression and secretion of human tissue plasminogen activator in the baculovirus system," *J. Biol. Chem. 268:* 16754-16762, 1993, teaches that deletion of the native signal sequence of human t-PA (tissue plasminogen activator) failed to increase t-PA production in a heterologous system. Page 16759 and Figure 8. Replacement of the signal sequence with signal sequences from three different

proteins also did not increase t-PA production. Jarvis concludes that other factors are involved in preventing high level production. See Abstract.

Berges *et al.*, "Combined effects of the signal sequence and the major chaperone proteins on the export of human cytokines in *Escherichia coli*," *App. and Env. Microbiol., 62:* 55-60, 1996, teaches that various combinations of signal peptides and proteins provide variable and unpredictable results. Some combinations are several-fold more efficiently translated than others. Some combinations lead to rapid growth arrest followed by slow cellular lysis. See page 49, discussion. These variations in expression among constructs employing the same signal sequence demonstrate that the identity and nature of the protein linked to the signal sequence influences heterologous expression efficiency in ways that are not predictable and do not depend solely on the presence or absence of a signal sequence.

The hypothetical person of ordinary skill would have been aware of at least these three publications and would have known that the effect of a signal sequence on the expression of cloned genes in heterologous host cells was unpredictable.

D. The Examiner has not made any of the required three showings for a *prima facie* case of obviousness.

The U.S. Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness. Only when a *prima facie* case has been established does the burden shift to the applicants to provide evidence or argument in rebuttal. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). In this case, the results of the factual inquiries carried out under *Graham* do not support a *prima facie* case that claims 1-49 of Serial No. 09/659,379 are obvious over claims 1-24 of the present application. The Examiner has not made any of the required three showings for a *prima facie* case of obviousness.

First, a *prima facie* case of obviousness requires a showing that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contain a suggestion or motivation to modify the reference teachings. M.P.E.P. § 2142. The problem the 09/659,379 invention solves is obtaining expression of copious amounts of INGAP protein from a cloned INGAP gene in a heterologous host cell. The present application in contrast does not even recognize the problem of poor expression of the cloned INGAP gene in a heterologous host cell. It thus does not teach or suggest any ways to overcome the problem. There is nothing in the present application's claims that teaches or suggests that the nucleotide sequence encoding the signal sequence should be removed. There is nothing in the present application's claims that indicates that removal of the coding sequence for the signal sequence would lead to improved expression levels.

Second, a *prima facie* case of obviousness requires a showing of a reasonable expectation of success in making the modification. Even if *arguendo* there existed a suggestion or motivation to modify the teachings of claims 1-8, 15, 16, and 18-22 or claims 9-14, 17, 23, and 24 of the present application to exclude the signal sequence of the recited INGAP, those of skill in the art would not have had a reasonable expectation that such removal would have successfully increased expression levels. As discussed above, the prior art indicates that there is significant unpredictability in expressing proteins in a heterologous host cell. Deletion of a signal sequence could be deleterious, leading to an unstable mRNA. See Xu, *supra.* Deletion of a signal sequence could fail to increase production of a protein in a heterologous system. See Jarvis, *supra.* The identity and nature of the protein can affect the levels of expression in ways that were unpredictable at the time the invention was made. See Berges, *supra.* Thus, prior to

the invention of the 09/659,379 application, it would not have been obvious that removing the signal sequence of INGAP would lead to increased production of INGAP in heterologous host cells.

Third, a *prima facie* case of obviousness requires showings that claims 1-8, 15, 16, and 18-22 and that claims 9-14, 17, 23, and 24 teach or suggest all the limitations of claims 1-49. Claims 1-8, 15, 16, and 18-22 of the present application cannot suggest removing the amino acids of the signal sequence from the recited amino acid sequence because claims 1-8, 15, 16, and 18-22 explicitly require a nucleotide sequence encoding the full-length INGAP pre-protein. Claims 9-14, 15, 16, and 18-22 of the present application contain no suggestion to remove the amino acids of the signal sequence from the recited amino acid sequence because they do not recite any particular portion of SEQ ID NO:2 that should be included or excluded. Thus, neither claims 1-8, 15, 16, and 18-22 nor claims 9-14, 17, 23, and 24 teach or suggest all the elements in claims 1-49 of the 09/659,379 application.

A *prima facie* case of obviousness would fail if any one of the required three showings failed. In the present application, the Examiner has made none of the required three showings. Thus, a *prima facie* case of obviousness has not been made. Indeed, the facts discussed above prevent such showings.

In a two-way test for obviousness-type double patenting, if either set of claims is not obvious over the other, a double patenting rejection cannot be maintained. Because copending claims 1-49 would not have been obvious over either claims 1-8, 15, 16, and 18-22 or claims 9-14, 17, 23, and 24 of the present application, there is no basis for an obviousness-type double patenting rejection of claims 1-24.

## CONCLUSION

The office actions in this application have repeatedly asserted that the claimed subject matter in the present application is an obvious variation of that claimed in Serial No. 09/659,379. *See, e.g.,* Paper No. 19, page 5, lines 1-2. The office actions have never provided any analysis that compares the properly construed claims or developed any reasoning as to why the claims of one application would be obvious over the other. As the M.P.E.P. explains,

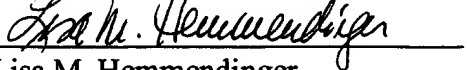
> [m]erely asserting that two sets of claims are obvious over each other is insufficient to make a *prima facie* case. "Any obviousness-type double patenting rejection should make clear: (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent."

M.P.E.P., 8th ed., § 804 (II)(B)(1). Contrary to the clear instructions in the M.P.E.P. and in the law, the Examiner has erroneously compared sequences disclosed in each specification but has failed to compare the properly construed claims including all of their recitations. Nor has the Examiner made even a bare assertion of why a person of ordinary skill in the art would conclude that the invention defined by claims 1-49 of Serial No. 09/569,379 is an obvious variation of the invention claimed in the present application. No basis for that conclusion exists in the facts.

The Board of Patent Appeals and Interferences should reverse the obviousness-type double patenting rejection of claims 1-24.

Respectfully submitted,
BANNER & WITCOFF, LTD.

Date: June 25, 2004

By: 
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## APPENDIX 1. CLEAN COPY OF APPEALED CLAIMS

1. An isolated DNA molecule encoding a mammalian islet cell neogenesis associated protein (INGAP), wherein the INGAP has the amino acid sequence shown in SEQ ID NO: 2.

2. The DNA molecule of claim 1 which has the nucleotide sequence shown in SEQ ID NO: 1.

3. A vector comprising the DNA of claim 1.

4. The vector of claim 3 further comprising expression control sequences, whereby said DNA is expressed in a host cell.

5. The vector of claim 4 which comprises an Epstein Barr Nuclear Antigen-Histidine (EBNA His) plasmid.

6. A host cell transformed with the DNA of claim 1.

7. A host cell transformed with the vector of claim 3.

8. The host cell of claim 6 which is a cos7, African Green Monkey kidney cell.

9. A nucleotide probe comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian islet cell neogenesis associated protein (INGAP), wherein said protein has the sequence shown in SEQ ID NO: 2.

10. The nucleotide probe of claim 9 wherein the nucleotide sequence encoding a mammalian INGAP has the sequence shown in SEQ ID NO: 1.

11. The nucleotide probe of claim 9 wherein said probe is labeled with a detectable moiety.

12. An isolated DNA molecule comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian islet cell neogenesis associated protein (INGAP), wherein said protein has the sequence shown in SEQ ID NO: 2, wherein said DNA molecule encodes a polypeptide which stimulates islet cell neogenesis.

13. The DNA molecule of claim 12 wherein the sequence encoding the mammalian INGAP has the sequence shown in SEQ ID NO: 1.

14. The DNA molecule of claim 12 wherein said molecule is labeled with a detectable moiety.

15. A method of producing a mammalian INGAP, comprising the steps of:

providing a host cell according to claim 6;

culturing the host cell in a nutrient medium so that the INGAP is expressed; and

harvesting the INGAP from the host cells or the nutrient medium.

16. A method of producing a mammalian INGAP, comprising the steps of:

providing a host cell comprising the DNA molecule of claim 1;

culturing the host cell in a nutrient medium so that the mammalian INGAP is expressed; and

harvesting the mammalian INGAP from the host cells or the nutrient medium.

17. An antisense construct of a mammalian islet cell neogenesis associated protein (INGAP) gene comprising:

a promoter, a terminator, and a nucleotide sequence which encodes all or a portion of a protein as shown in SEQ ID NO: 2, said nucleotide sequence being between said promoter and said terminator, said nucleotide sequence being inverted with respect to said promoter, whereby upon expression from said promoter an mRNA complementary to native mammalian INGAP mRNA is produced, wherein said mRNA complementary to native mammalian INGAP mRNA prevents translation of the native mammalian INGAP mRNA.

18. The DNA molecule of claim 1 wherein the INGAP is from human.

19. The DNA molecule of claim 1 which comprises nucleotides 4 to 268 and 389 to 629 of SEQ ID NO:1.

20. A vector comprising the DNA of claim 2.

21. A host cell transformed with the vector of claim 20.

22. The DNA molecule of claim 1 which is a cDNA molecule.

23. The DNA molecule of claim 12 which is a cDNA molecule.

24. The DNA molecule of claim 12 which encodes a portion of INGAP, wherein said DNA molecule encodes a polypeptide which stimulates islet cell neogenesis.

## APPENDIX 2. APPEALED CLAIMS SHOWING HOW THEY DIFFER FROM ISSUED U.S. PATENT 5,840,531

1. An isolated DNA molecule encoding a mammalian islet cell neogenesis associated protein (INGAP) [protein], wherein the INGAP [protein] has the amino acid sequence shown in SEQ ID NO: 2.

2. The DNA molecule of claim 1 [wherein the INGAP protein] which has the nucleotide sequence shown in SEQ ID NO: 1.

3. A vector comprising the DNA of claim 1.

4. The vector of claim 3 further comprising expression control sequences, whereby said DNA is expressed in a host cell.

5. The vector of claim 4 which comprises [a] an Epstein Barr Nuclear Antigen-Histidine (EBNA His) plasmid.

6. A host cell transformed with the DNA of claim 1.

7. A host cell transformed with the vector of claim 3.

8. The host cell of claim 6 which is a cos7, African [cos7,African]Green Monkey kidney cell.

9. A nucleotide probe comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian islet cell neogenesis associated protein (INGAP), wherein said protein has the sequence shown in SEQ ID NO: 2.

10. The nucleotide probe of claim 9 wherein the nucleotide sequence encoding a mammalian INGAP [gene] has the sequence shown in SEQ ID NO: 1.

11. The nucleotide probe of claim 9 wherein said probe is labeled with a detectable moiety.

12. [A] An isolated DNA molecule comprising at least 30 contiguous nucleotides of a sequence encoding a mammalian islet cell neogenesis associated protein (INGAP), wherein said protein

has the sequence shown in SEQ ID NO: 2, wherein said DNA molecule encodes a polypeptide which stimulates islet cell neogenesis.

13. The DNA molecule of claim 12 wherein the sequence encoding the mammalian INGAP [gene] has the sequence shown in SEQ ID NO: 1.

14. The DNA molecule of claim 12 wherein said molecule is labeled with a detectable moiety.

15. A method of producing a mammalian INGAP [protein], comprising the steps of:

providing a host cell according to claim 6;

culturing the host cell in a nutrient medium so that the INGAP [protein] is expressed; and

harvesting the INGAP [protein] from the host cells or the nutrient medium.

16. A method of producing a mammalian INGAP [protein], comprising the steps of:

providing a host cell comprising the DNA molecule of claim 1;

culturing the host cell in a nutrient medium so that the mammalian INGAP [protein] is expressed; and

harvesting the mammalian INGAP [protein] from the host cells or the nutrient medium.

17. An antisense construct of a mammalian islet cell neogenesis associated protein (INGAP) gene comprising:

a promoter, a terminator, and a nucleotide sequence [consisting of a mammalian INGAP gene, wherein the gene] which encodes all or a portion of a protein as shown in SEQ ID NO: 2, said nucleotide sequence being between said promoter and said terminator, said nucleotide sequence being inverted with respect to said promoter, whereby upon expression from said promoter an mRNA complementary to native mammalian INGAP mRNA is produced, wherein said mRNA complementary to native mammalian INGAP mRNA prevents translation of the native mammalian INGAP mRNA.

18. The DNA molecule of claim 1 wherein the INGAP [protein] is from human.

19. The DNA molecule of claim 1 which comprises nucleotides 4 to 268 and 389 to 629 of SEQ ID NO:1.

20. A vector comprising the DNA of claim 2.

21. A host cell transformed with the vector of claim 20.

22. The DNA molecule of claim 1 which is a cDNA molecule.

23. The DNA molecule of claim 12 which is a cDNA molecule.

24. The DNA molecule of claim 12 which encodes a portion of INGAP, wherein said DNA molecule encodes a polypeptide which stimulates islet cell neogenesis.

## APPENDIX 3. CLEAN COPY OF PENDING CLAIMS OF SERIAL NO. 09/659,379

1. A recombinant construct for expression of a protein which stimulates islet cell neogenesis comprising:

a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5′ of said first nucleotide sequence.

2. The construct of claim 1 wherein nucleotides 1-16 of SEQ ID NO: 1 are not present 5′ of said first nucleotide sequence.

3. The construct of claim 1 further comprising a third nucleotide sequence encoding a histidine tag.

4. The construct of claim 3 wherein the third nucleotide sequence is immediately 5′ or 3′ to said first nucleotide sequence.

5. The construct of claim 1 wherein the transcriptional initiation site is inducible.

6. The construct of claim 1 wherein the transcriptional initiation site is the lac promoter and operator.

7. The construct of claim 1 wherein the transcriptional initiation site is capable of initiating constitutive transcription.

8. The construct of claim 7 wherein the transcriptional initiation site is Rous sarcoma virus long terminal repeat (RSVLTR).

9. The construct of claim 1 further comprising a nucleotide sequence encoding a nuclear antigen.

10. The construct of claim 9 wherein the nuclear antigen is Epstein-Barr nuclear antigen-1 (EBNA-1).

11. The construct of claim 1 further comprising an origin of replication.

12. The construct of claim 11 wherein the origin of replication is Epstein Bar Virus (EBV) origin of replication.

13. A method of producing biologically active Islet Neogenesis Associated Protein or INGAP from a recombinant host cell comprising the steps of:

culturing a host cell comprising a recombinant construct comprising a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5′ of said first nucleotide sequence, and

recovering protein from said cultured host cell.

14. The method of claim 13 wherein the construct further comprises a third nucleotide sequence encoding a histidine tag, and INGAP is purified using a nickel affinity matrix.

15. A host cell comprising a recombinant construct comprising a first nucleotide sequence encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5′ of said first nucleotide sequence.

16. The construct of claim 1 wherein the first nucleotide sequence encoding amino acid residues 27 to 175 comprises nucleotides 12-458 of SEQ ID NO: 4.

17. The method of claim 13 wherein the first nucleotide sequence encoding amino acid residues 27-175 comprises nucleotides 12-458 of SEQ ID NO: 4.

18. The host cell of claim 15 wherein the first nucleotide sequence encoding amino acid residues 27-175 comprises nucleotides 12-458 of SEQ ID NO: 4.

19. The construct of claim 1 wherein the transcriptional initiation site is selected from the group consisting of: λcI promoter, tac promoter, trp promoter, and tet promoter.

20. The construct of claim 1 which comprises a nucleotide sequence as shown in SEQ ID NO: 4.

21. A pair of oligonucleotide primers for amplifying a coding sequence consisting of nucleotides 12 to 458 of SEQ ID NO: 4, wherein each of said oligonucleotide primers hybridizes to an opposite strand of a double-stranded INGAP template under conditions sufficient for amplifying, wherein a first of said oligonucleotide primers hybridizes to the 5′ end of the coding sequence for mature human INGAP and the second of said oligonucleotide primers hybridizes to the 3′ end of the nucleotide sequence encoding mature human INGAP under conditions sufficient for amplifying nucleotides 12 to 458 of SEQ ID NO: 4.

22. The pair of oligonucleotide primers of claim 21 wherein one primer has the nucleotide sequence shown in SEQ ID NO: 2 and one primer has the nucleotide sequence shown in SEQ ID NO: 3.

23. A method of making an expression construct for producing INGAP in a recombinant host cell, comprising the step of:

linking a transcription initiation site, a translation initiation site, and a coding sequence for mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4, to make an expression construct which is devoid of the signal sequence of the coding sequence of INGAP.

24. The method of claim 23 further comprising linking to said coding sequence for mature human INGAP a coding sequence for a histidine tag.

25. The method of claim 23 wherein the transcription initiation site is inducible.

26. The method of claim 25 wherein the transcription initiation site is selected from the group consisting of the lac promoter/operator, the tac promoter, the trp promoter, the λcI promoter, and the tet promoter.

27. The method of claim 23 wherein the coding sequence for mature human INGAP is obtained by amplification of a coding sequence consisting of nucleotides 12 to 458 of SEQ ID NO: 4.

28. The method of claim 27 wherein the amplification is performed using primers having sequences as shown in SEQ ID NO: 2 and SEQ ID NO: 3.

29. A recombinant construct comprising:

a first nucleotide sequence encoding mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4, said first nucleotide sequence being operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5' of said first nucleotide sequence.

30. The construct of claim 29 wherein nucleotides 1-16 of SEQ ID NO: 1 are not present 5' of said first nucleotide sequence.

31. The construct of claim 29 further comprising a third nucleotide sequence encoding a histidine tag.

32. The construct of claim 29 wherein the third nucleotide sequence is immediately 5' or 3' to said first nucleotide sequence.

33. The construct of claim 29 wherein the transcriptional initiation site is inducible.

34. The construct of claim 33 wherein the transcriptional initiation site is the lac promoter/operator.

35. The construct of claim 29 wherein the transcriptional initiation site is capable of initiating constitutive transcription.

36. The construct of claim 35 wherein the promoter sequence is Rous sarcoma virus long terminal repeat (RSVLTR).

37. The construct of claim 29 further comprising a nucleotide sequence encoding a nuclear antigen.

38. The construct of claim 37 wherein the nuclear antigen is Epstein-Barr nuclear antigen-1 (EBNA-1).

39. The construct of claim 29 further comprising an origin of replication.

40. The construct of claim 39 wherein the origin of replication is Epstein Bar Virus (EBV) origin of replication.

41. The construct of claim 33 wherein the transcriptional initiation site is the λcI promoter/operator.

42. The construct of claim 33 wherein the transcriptional initiation site is the trp promoter.

43. The construct of claim 33 wherein the transcriptional initiation site is the tac promoter.

44. The construct of claim 33 wherein the transcriptional initiation site is the tet promoter.

45. A method of producing biologically active Islet Neogenesis Associated Protein (INGAP) from a recombinant host cell comprising the steps of:

culturing a host cell comprising a recombinant construct comprising a first nucleotide sequence encoding mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5′ of said first nucleotide sequence; and

recovering protein from said cultured host cell.

46. The method of claim 45 wherein the construct further comprises a third nucleotide sequence encoding a histidine tag, and INGAP is purified using a nickel affinity matrix.

47. A host cell comprising a recombinant construct comprising a first nucleotide sequence encoding mature human INGAP operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5′ of said first nucleotide sequence.

48. The method of claim 23 wherein the coding sequence for mature human INGAP encodes amino acid residues 27 to 175 as shown in SEQ ID NO: 6.

49. The pair of oligonucleotide primers of claim 21 wherein the first of said oligonucleotide primers comprises nucleotides 12 to 31 of SEQ ID NO: 2 and the second of said oligonucleotide primers comprises nucleotides 13 to 32 of SEQ ID NO: 3.

## APPENDIX 4. COPY OF PENDING CLAIMS OF SERIAL NO. 09/659,379 SHOWING HOW THEY DIFFER FROM ISSUED U.S. PATENT 5,804,421

1. A recombinant construct for expression of a protein which stimulates islet cell neogenesis [Islet Neogenesis Associated Protein or INGAP activity] comprising:

a first nucleotide sequence encoding amino acid[s] residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5′ of said first nucleotide sequence.

2. The construct of claim 1 wherein nucleotides 1-16 of SEQ ID NO: 1 are not present 5′ of said first nucleotide sequence.

3. The construct of claim 1 further comprising a third nucleotide sequence encoding a histidine tag.

4. The construct of claim 3 wherein the third nucleotide sequence is immediately 5′ or 3′ to said first nucleotide sequence.

5. The construct of claim 1 wherein the transcriptional initiation site is inducible.

6. The construct of claim 1 wherein the transcriptional initiation site is the lac promoter [/] and operator.

7. The construct of claim 1 [further comprising a promoter sequence] wherein the transcriptional initiation site is capable of initiating constitutive transcription.

8. The construct of claim 7 wherein the [promoter sequence] transcriptional initiation site is Rous sarcoma virus long terminal repeat (RSVLTR).

9. The construct of claim 1 further comprising a nucleotide sequence encoding a nuclear antigen.

10. The construct of claim 9 wherein the nuclear antigen is Epstein-Barr nuclear antigen-1 (EBNA-1).

11. The construct of claim 1 further comprising an origin of replication.

12. The construct of claim 11 wherein the origin of replication is Epstein Bar Virus (EBV) origin of replication.

13. A method of producing biologically active Islet Neogenesis Associated Protein or INGAP [protein] from a recombinant host cell comprising the steps of:

culturing a host cell comprising a recombinant construct comprising a first nucleotide sequence encoding amino acid[s] residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5′ of said first nucleotide sequence, and

recovering protein from said cultured host cell.

14. The method of claim 13 wherein the construct further comprises a third nucleotide sequence encoding a histidine tag, and INGAP [protein] is purified using a nickel affinity matrix.

15. A host cell comprising a recombinant construct comprising a first nucleotide sequence encoding amino acid[s] residues 27 to 175 as shown in SEQ ID NO: 6 operably linked to a transcriptional [iron] initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide is not present immediately [5+] 5′ of said first nucleotide sequence.

16. The construct of claim 1 wherein the first nucleotide sequence encoding amino acid[s] residues 27 to 175 comprises nucleotides 12-458 [12-456] of SEQ ID NO: 4.

17. The method of claim 13 wherein the first nucleotide sequence encoding amino acid[s] residues 27-175 comprises nucleotides 12-458 [12-456] of SEQ ID NO: 4.

18. The host cell of claim 15 wherein the first nucleotide sequence encoding amino acid[s] residues 27-175 comprises nucleotides 12-458 [12-456] of SEQ ID NO: 4.

19. The construct of claim 1 wherein the transcriptional initiation site is selected from the group consisting of: λcI promoter, tac promoter, trp promoter, and tet promoter.

20. The construct of claim 1 which comprises a nucleotide sequence as shown in SEQ ID NO: 4.

21. A pair of oligonucleotide primers for amplifying a coding sequence consisting of nucleotides 12 to 458 of SEQ ID NO: 4, wherein each of said oligonucleotide primers hybridizes to an opposite strand of a double-stranded INGAP template under conditions sufficient for amplifying, wherein a first of said oligonucleotide primers hybridizes to the 5′ end of the coding sequence for mature human INGAP and the second of said oligonucleotide primers hybridizes to the 3′ end of the nucleotide sequence encoding mature human INGAP under conditions sufficient for amplifying nucleotides 12 to 458 of SEQ ID NO: 4.

22. The pair of oligonucleotide primers of claim 21 wherein one primer has the nucleotide sequence shown in SEQ ID NO: 2 and one primer has the nucleotide sequence shown in SEQ ID NO: 3.

23. A method of making an expression construct for producing INGAP in a recombinant host cell, comprising the step of:

linking a transcription initiation site, a translation initiation site, and a coding sequence for mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4, to make an expression construct which is devoid of the signal sequence of the coding sequence of INGAP.

24. The method of claim 23 further comprising linking to said coding sequence for mature human INGAP a coding sequence for a histidine tag.

25. The method of claim 23 wherein the transcription initiation site is inducible.

26. The method of claim 25 wherein the transcription initiation site is selected from the group consisting of the lac promoter/operator, the tac promoter, the trp promoter, the λcI promoter, and the tet promoter.

27. The method of claim 23 wherein the coding sequence for mature human INGAP is obtained by amplification of a coding sequence consisting of nucleotides 12 to 458 of SEQ ID NO: 4.

28. The method of claim 27 wherein the amplification is performed using primers having sequences as shown in SEQ ID NO: 2 and SEQ ID NO: 3.

29. A recombinant construct comprising:

a first nucleotide sequence encoding mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4, said first nucleotide sequence being operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5' of said first nucleotide sequence.

30. The construct of claim 29 wherein nucleotides 1-16 of SEQ ID NO: 1 are not present 5' of said first nucleotide sequence.

31. The construct of claim 29 further comprising a third nucleotide sequence encoding a histidine tag.

32. The construct of claim 29 wherein the third nucleotide sequence is immediately 5' or 3' to said first nucleotide sequence.

33. The construct of claim 29 wherein the transcriptional initiation site is inducible.

34. The construct of claim 33 wherein the transcriptional initiation site is the lac promoter/operator.

35. The construct of claim 29 wherein the transcriptional initiation site is capable of initiating constitutive transcription.

36. The construct of claim 35 wherein the promoter sequence is Rous sarcoma virus long terminal repeat (RSVLTR).

37. The construct of claim 29 further comprising a nucleotide sequence encoding a nuclear antigen.

38. The construct of claim 37 wherein the nuclear antigen is Epstein-Barr nuclear antigen-1 (EBNA-1).

39. The construct of claim 29 further comprising an origin of replication.

40. The construct of claim 39 wherein the origin of replication is Epstein Bar Virus (EBV) origin of replication.

41. The construct of claim 33 wherein the transcriptional initiation site is the λcI promoter/operator.

42. The construct of claim 33 wherein the transcriptional initiation site is the trp promoter.

43. The construct of claim 33 wherein the transcriptional initiation site is the tac promoter.

44. The construct of claim 33 wherein the transcriptional initiation site is the tet promoter.

45. A method of producing biologically active Islet Neogenesis Associated Protein (INGAP) from a recombinant host cell comprising the steps of:

culturing a host cell comprising a recombinant construct comprising a first nucleotide sequence encoding mature human INGAP consisting of nucleotides 12 to 458 of SEQ ID NO: 4 operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5′ of said first nucleotide sequence; and

recovering protein from said cultured host cell.

46. The method of claim 45 wherein the construct further comprises a third nucleotide sequence encoding a histidine tag, and INGAP is purified using a nickel affinity matrix.

47. A host cell comprising a recombinant construct comprising a first nucleotide sequence encoding mature human INGAP operably linked to a transcriptional initiation site and a translational initiation site, wherein a second nucleotide sequence encoding a signal peptide according to SEQ ID NO: 5 is not present immediately 5′ of said first nucleotide sequence.

48. The method of claim 23 wherein the coding sequence for mature human INGAP encodes amino acid residues 27 to 175 as shown in SEQ ID NO: 6.

49. The pair of oligonucleotide primers of claim 21 wherein the first of said oligonucleotide primers comprises nucleotides 12 to 31 of SEQ ID NO: 2 and the second of said oligonucleotide primers comprises nucleotides 13 to 32 of SEQ ID NO: 3.